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JTH COMMENTARY

Antibody-mediated platelet activation in COVID-19: A coincidence or a new mechanism of the dysregulated coagulation system?

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In this issue of *JTH*, Nazy and colleagues report on antibody-mediated platelet activation as a driver of thrombosis in coronavirus disease 2019 (COVID-19) infection.[1] During the pandemic, and despite the lockdown, the authors made use of a routine assay that uses washed platelets to investigate antibody-mediated platelet activation. They found that sera from critically ill COVID-19 patients have the ability to activate platelets via crosslinking their Fc-gamma (y)-receptor (R) IIa.

Although there are enormous numbers of publications on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, yet the mystery of high incidences of micro- and macrovascular thromboembolic events despite anticoagulant therapy in critically ill COVID-19 patients remains unsolved. Interestingly, because COVID-19 is occasionally accompanied by thrombocytopenia, the thrombotic phenotype shows some similarity with heparin-induced thrombocytopenia (HIT).[2,3] In fact, SARS-CoV-2 infection has been described to be associated with platelet hyperreactivity, which may contribute to thromboembolic complications in COVID-19.[4] Consequently, the authors followed the idea to explore the role of FcγRIIa in platelet activation by serum of COVID-19 patients. In sera from COVID-19 patients with suspected HIT, Nazy et al. found platelet activation using the serotonin release assay, which is a function of the HIT test. Although platelet activation was inhibited by high concentration of heparin (a typical serological pattern of clinically relevant HIT antibodies), no heparin-PF4 antibodies were detected in these sera, which excludes HIT. Elegantly, the authors used an FcγRIIa-blocking monoclonal antibody (mAb IV.3) to explore the mechanism of platelet activation. The release of serotonin was completely inhibited by mAb IV.3 indicating that immunoglobulin G (IgG) antibodies, most likely bound in immune complexes (ICs) crosslink FcγRIIa receptors to induce platelet activation (Figure 1). Accordingly, the authors postulate an IC-mediated process comparable to the one previously described in H1N1 viral infection.[5] These findings are in line with our recent work published almost at the same time. We found that platelets from severe COVID-19 patients have an upregulation of platelet procoagulant markers, such as externalization of phosphatidylserine. Most importantly, we observed that sera from these patients are able to induce a procoagulant phenotype in platelets from healthy donors. We showed that IgG from patients with severe COVID-19 triggers the formation of procoagulant platelets via FcγRIIa.[6] This mechanism is also induced by ICs and not only by an antibody-mediated pathway. ICs are known to trigger endothelial cell activation in HIT and in lupus vasculitis.[7,8] For future experiments, it would be interesting to differentiate between IgG antibodies specific against platelets (as previously reported for Dengue infections[9]) and circulating ICs that activate platelets in lupus.[10] This can be easily done by testing purified IgG fractions from patient's sera or treating sera by polyethylene glycol to remove unspecific immune complexes. Awaiting the results from these studies, the observations of Nazy et al. and our recent study indicate an important aspect of antibody-mediated platelet activation in the thromboinflammation during infection diseases such as, but not limited to, COVID-19.[11]

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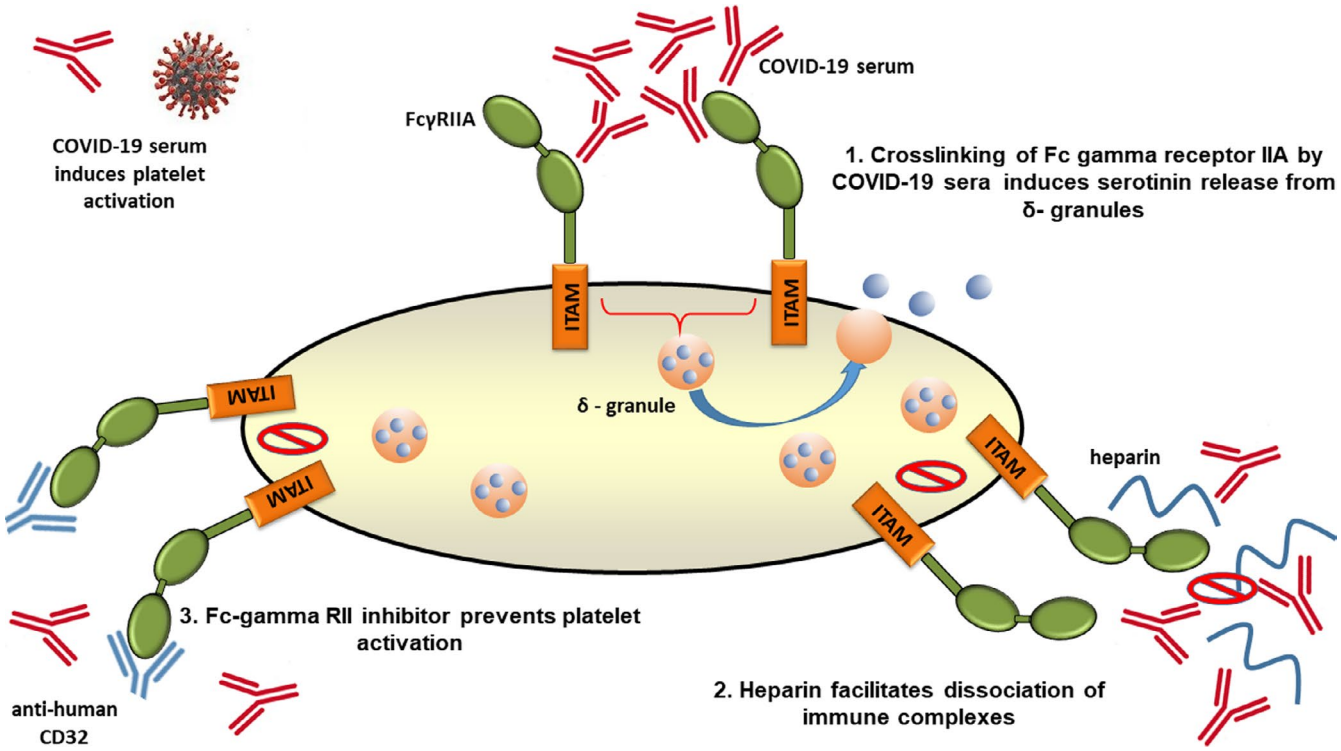

FIGURE 1 COVID-19 sera induce platelet activation. Crosslinking of Fc gamma receptor IIA by COVID-19 sera induces serotonin release from δ-granules. This can be inhibited by heparin and anti-human CD32 (IV.3). COVID, coronavirus disease 2019

The study of Nazy and colleagues has several clinical implications. First of all, HIT seems to be infrequent in critically ill COVID-19 patients. Brodard et al. suggested that COVID-19 patients have high-titer antibodies against heparin-PF4 complexes.[12] In the study of Nazy et al., platelet activation was observed in the absence of detectable PF4/heparin. These findings emphasize that the diagnosis of HIT requires both of the detection of the specific antibodies and the confirmation of heparin-dependent, platelet-activating antibodies to avoid overdiagnosis. Nazy et al. used a commercially available immunoassay that detects only PF4/heparin antibodies. Immunization against other heparin-dependent antigens such as interleukin-8 cannot be excluded.[13] Nevertheless, SARS-CoV-2 antibodies are the most promising candidates to form such ICs in COVID-19.

Second, the safety of convalescent plasma from noncritically ill COVID-19 subjects was a concern of this study and others.[6] Sera from donors of convalescent plasma did not activate platelets. The authors indicate that the antibodies against the Spike-protein receptor-binding domain might not be involved in the pathophysiology or there might be another unknown plasma factor. Interestingly, the serum with the highest reactivity in the serotonin release assay is one with the lowest reactivity in the anti–SARS-CoV-2 antibody assay. So, the question regarding the target of the antibody, which binds via FcγRIIa to activate platelets, remains unanswered.

Most importantly, Nazy et al. observed that platelet activation was reduced or suppressed by heparin. Serotonin release was reduced with all heparin concentrations (0.1, 0.3 U/ml and 100 U/ml). This might support current guidelines in starting antithrombotic therapy using heparin early for reduction of thromboembolic risk in patients with COVID-19 infection. The authors speculate binding of heparin to the SARS-CoV-2 receptor-binding domain might cause a conformational change and disrupt the immune complexes subsequently inhibiting platelet activation. This interesting hypothesis needs to be verified in future studies.

However, taken together, the findings by Nazy et al. support the role of platelets as one of the drivers in thromboembolic complications in SARS-CoV-2 infection.[6] The target of the IC-forming antibody remains unclear and further investigations are needed to solve this mystery. Inhibition of platelet activation by heparin in vitro supports the demand for early anticoagulation therapy in patients with severe infection.

CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

Karina Althaus, Jan Zlamal, and Tamam Bakchoul wrote the manuscript.

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